solution. However that method would not produce a coated powder having sustained release properties. While not wishing to be bound by theory the traditional teaching is that sustained release properties could not be obtained because the coating was too porous. The speculation was that the porous coating resulted because of the formation of blow holes in the final coating. While not necessarily deleterious to the taste masking properties of the coating such a porous coating compromised the sustained release properties. Therefore, the conventional wisdom was that a spray drying process would not produce a particle having both adequate taste masking and sustained release properties. See the previously submitted Deasy article.

In contrast to that teaching, Applicants have overcome these problems as evidenced by the bioavailability study shown in Table 2 which demonstrates that the powders of the present invention provide sustained release properties when compared to non-coated products. Accordingly the present invention provides a significant improvement over the prior art.

Claims 16 to 25 and 27 to 30 have been rejected under 35 U.S.C. 102(b) as anticipated by CA 2,068,366 (CA'366). Claims 16 to 20, 22 to 24 and 26 have been rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,808,411 to Lu. It is submitted both these rejections are improper and should be withdrawn.

For a single reference to anticipate a claimed invention, that reference must show each and every feature of the claimed invention and those features must be arranged as in the claimed invention. Thus, neither CA '366 nor the '411 patent are anticipatory as a matter of law and the rejections under 35 U.S.C. § 102 are in error as a matter of law. See Connell v. Sears Roebuck & Co., 220 U.S.P.Q. 193 (Fed. Cir. 1983).

Neither CA '366 nor Lu '411 disclose a formulation of the invention as defined by the now pending claims. At a minimum, neither reference slows or suggests the features of the particles.

The Lu '411 reference discloses a complex of carbomer (acrylic acid polymers) and erythromycin or a derivative thereof. Lu's compositions are prepared by dispersing the drug, such as erythromycin, in a suitable organic solvent such as ethanol or acetone, and dispersing the carbomer separately in ethanol, mixing the two solutions slowly to allow formation of the reaction product and then evaporating most of the solvent and diluting the solution with water. The reaction product is recovered by filtration and is then dried. This reference gives no indication of the weight percent of the coating. The Examiner apparently cites Lu for its disclosure of particle size range. However, none of the particle size ranges disclosed in Lu correspond with, or suggest, those set forth in the pending claims. A mention in a reference of particles smaller than 297 microns does not disclose or suggest the parameters set forth in the claims.

The Examiner states "because neither of the references mention any limitation on the shape of the particles, the formulations of the prior art inherently encompass any suitable shape with any suitable aspect criteria. Therefore, the limitations of aspect ratio and spherical shape of particies as instantly claimed are not considered critical and do not render the claims patentable over the prior art."

The silence of a reference as to a feature cannot be equated with an inherent disclosure as to every possible variation of an undisclosed feature. Inherency only applies when a particular feature property or aspect must be that as claimed not when it is one of many possibilities.

Applicants have discovered that there are a number of important interacting parameters that effect the taste masking of a pharmaceutical. Applicants have found that shape, aspect ratio, particles size and the particle size distribution utilized in the process have a significant effect on the performance characteristics. Applicants also have noted that in many cases it is the interaction of these parameters that influences the ultimate success of the process. Thus, control of only one parameter will not necessarily be adequate. What is important is that the combination of parameters be selected to provide the desired properties of the compositions.

As illustrated in CA '366, the prior art did not consider aspect ratio, shape, size of the particles and/or the particle size distribution as significant. While CA '366 maintains preferred particle sizes, other aspects of the of the particles such as shape or aspect ratio were not addressed. Thus, the disclosure of CA '366 could result in products having inconsistent release and taste masking characteristics.

Applicants discovered that the presence of "fine" drug particles leads to an increased rate of drug release after coating with polymer. This was thought to be due to the increased drug surface area that in turn led to a thinner polymer coating when common amounts of polymer were utilized. Initially, the Applicants thought that it was the control of drug particle size that was the only important factor as did others in the art. Applicants discovered that particle shape was potentially an important parameter. Two test batches D4426 and D4427 were treated to determine the effect of needle shaped particles. Attached to the enclosed Lukas declaration are electron micrographs of powder of test batches D4426 and D4427. Batch D4426 was utilized as supplied by the supplier. As can be readily seen from the electron micrograph in Batch D4426 (which details the material provided by the supplier) a certain number of particles are effectively oblong in shape and contain sharp edges and are outside the

now claimed aspect ratio. In contrast, the electron micrograph of Batch D4427 does not demonstrate particles with these dimensions. Further, a more homogenous particle size distribution also improves the performance characteristics. When these batches of particles were subjected to the process described, it was found that the needle shaped particles produced a material where 19% of the material was released after 40 minutes which is unacceptably high. In contrast, the more homogenous batch D4427 only demonstrate 8% release after 40 minutes. This was therefore an acceptable release profile. The results of these trials are discussed in the enclosed Lukas declaration.

In summary, Applicants have discovered the parameters in relation to the use of a small amount of polymer coating to successfully achieve taste masking and sustained release properties for pharmaceutically active compounds. These parameters include control of the shape of the core particle which leads to a product with successful performance characteristics. Neither CA '366 or Lu disclose or suggest this important feature and accordingly, it is respectfully submitted that the claims are not anticipated or rendered obvious by the cited prior art.

Claims 16 to 30 were rejected under 35 U.S.C. 103(a) as unpatentable over CA'366 in combination with either '411 or U.S. Patent No. 5,707,646 to Yajima et al. (Yajima). It is submitted the rejection is improper and should be withdrawn.

CA '366 and Lu '411 have been discussed above and those comments should be considered as if here set forth.

Nothing in the Office Action discussing the Yajima reference or in the reference itself indicates that a substantially continuous polymer coating is formed and that the resulting product

has sustained release properties or that the coating comprises less than 23% by weight of the formulation.

Yajima relates to a taste masked pharmaceutical formulation comprising clarithromycin. The spray drying process as described in the present application as understood by one skilled in the art involves the dispersion of the active constituents and the polymeric coating in a solvent followed by evaporation of the solvent through the use of a spray dryer. Generally the solubility of the drug to be used in the solvent is lower than the solubility of the coating agent in the solvent. Accordingly, as the solvent particles evaporate the active agents crystallize and a liquid coating, which comprises the solvent and the still dissolved coating polymer, form about them. With continued solvent evaporation the coating polymer is no longer soluble in the remaining solvent and crystallizes forming a continuous polymer coating around the active drug (which acts as a seed crystal for the polymer). This leads to the improved coating properties of the present invention as it affords almost a discrete core of active constituent surrounded by a discrete polymer coating. · Furthermore, in some cases of spray drying the solvent is chosen so as not to dissolve the active ingredient at all i.e. the active ingredient stays crystalline throughout the process, and during the spray drying process the polymeric coating dries around the already crystalline active ingredient.

In contrast, Yajima's process, illustrated in patent Example 1, while using a spray dryer apparatus does not conduct a conventional spray drying process. In actuality, Yajima describes the use of the spray dryer as a means of conducting a spray cooling operation to form a granulate. Thus, no solvent is used and the examples merely describe the situation where two polymers are heated above their melting point and clarithromycin is then dispersed therein. Following this dispersion the material is pumped through the apparatus to atomize it into small

particles which on cooling solidify to form granules. Thus, Yajima uses the apparatus for heat transfer only, not for mass transfer or a combined heat/mass transfer operation.

In Yajima, there is no spray drying *per se* occurring and therefore there is no assurance in this method that a continuous polymer coating on the active ingredients will be achieved. Indeed, there is an equal probability that the active particles would be on the surface of the granulate as opposed to the present invention which leads to all active particles having a polymeric coating thereon. Accordingly, it is submitted that Yajima does not disclose the subject matter of the now claimed invention. There is simply no teaching of, *inter alia,* the spray drying or the coating weight of the formulation.

As to either of the combinations, none of the references, alone or in combination teach the critical shape or aspect ratio of the particles claimed in the present claims. As also discussed above, it is this combination of shape along with control of the particle size distribution to predominantly be in a pre-defined range that provides improvements over the prior art, namely, the improved release properties. There is simply no teaching or suggestion in any of the cited references as to the importance of this ratio and/or particle size distribution or that these features would consistently provide a product with improved performance characteristics.

It is further submitted that the combinations of references are improper. As discussed above, each of the references list different techniques to obtain different products with different characteristics. It is clear that the Examiner has engaged in a pick and choose technique based on hindsight using Applicants' invention as a blueprint to selectively edit the cited references. This is improper. See In re Grabiak, 226 U.S.P.Q. 870 (Fed. Cir. 1985). Further, the manner in which the Examiner has edited the references for the combination would require that salient

features of the respective disclosures of the references and important features of the invention as disclosed therein be ignored. This is also improper for a rejection under 35 U.S.C. § 103. See In re Ratti, 123 U.S.P.Q. 349 (CCPA 1959).

As shown above, based on the prior art, the release and/or taste masking properties obtained were inconsistent which is not acceptable for pharmaceutical administration. In contrast by formulating formulations in accordance with the present invention, consistency of taste masking and sustained release is achieved, leading to improved results. See the enclosed Lukas Declaration. Accordingly, it is respectfully submitted that the invention is not obvious in view of the art.

In view of the foregoing, reconsideration and allowance of the application with claims 16 to 30 are earnestly solicited.

The Examiner is invited after reviewing the foregoing to phone Applicants' undersigned attorney to advise of the status of the matter or to resolve any remaining issues.

It is believed that no fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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Dated: November 8, 2001

Enc. Claim Changes
Lukas Declaration

Serial No.: 09/177,427

AMENDMENTS TO THE CLAIMS SHOWING CHANGES

In the Claims:

16. (Amended) A pharmaceutical formulation comprising: spray dried powder particles having a core element containing one or more pharmaceutically active compounds and a substantially continuous polymeric coating thereon, both to taste mask and to provide sustained release of said one or more active compounds wherein the polymer coating comprises less than 23% by weight of the formulation, wherein said core has an aspect ratio of less than 3 and further wherein no more than 25wt.-% of the particles are less than 25 macrometers and no more than 2 wt.-% of the particles are over 250 macrometers.

27. (Amended) A method of preparing a formulation [comprising:] of spray dried powder particles having a core element containing one or more pharmaceutically active compounds and a substantially continuous polymeric coating thereon, both to taste mask and to provide sustained release of said one or more active compounds wherein the polymer coating comprises less than 23% by weight of the formulation [and wherein said core has an aspect ratio of less than 3], the method comprising;

mixing said core element and said coating in a diluent to form a mixture; and

spray drying said mixture to form a powder wherein said core has an aspect ratio of less than 3 and wherein no more than 25 wt.-% of particles are less than 25 micrometers and no more than 2 wt.-% of particles are over 250 micrometers.